Class of antibiotics can enhance gene-silencing tool

July 20 2008

A way to turn off one gene at a time has earned acceptance in biology laboratories over the last decade. Doctors envision the technique, called RNA interference, as a tool to treat a variety of diseases if it can be adapted to humans.

Emory University researchers have discovered that antibiotics known as fluoroquinolones can make RNA interference more effective in the laboratory and reduce potential side effects. The results will be published online this week in the journal *Nature Biotechnology*.

"The surprising aspect is that some fluoroquinolones have this previously unrecognized property," says senior author Peng Jin, PhD, assistant professor of human genetics at Emory University School of Medicine. "The good part is that doctors have years of experience treating bacterial infections with them, so they are generally considered safe."

The most powerful enhancer of RNA interference was enoxacin, which has been used to treat gonorrhea and urinary tract infections. The group of compounds also includes the widely used antibiotic ciprofloxacin. The antibiotics' effect on RNA interference appears to be chemically separate from their bacteria-killing activities.

Significant barriers still prevent RNA interference from working well in people, Jin says.

"The barriers include specificity and toxicity, as well as getting the RNA

to the right place in the body," he says. "If we can enhance how potent a given amount of RNA is and reduce dosage, we're tackling both specificity and toxicity."

Some studies have found that side effects come from the amount of RNA injected, which can trigger an anti-viral response, rather than from the genetic sequence of the RNA used.

Andrew Fire and Craig Mello received the 2006 Nobel Prize in Medicine for their discovery that short pieces of RNA, when introduced into cells, can silence a stretch of genetic code. Artificially introduced RNA hijacks machinery inside the cell called the RNA-induced silencing complex or RISC.

To probe how RISC works, Jin and his co-workers inserted a gene for a fluorescent protein into a cell line, and then added a short piece of RNA that incompletely silences the inserted gene. That way, if a potential drug tweaked the silencing process, the researchers could see it quickly.

They found that enoxacin can increase how well a gene is silenced by up to a factor of ten in cultured cells and by a factor of three in mice. It appears to strengthen the grip of part of RISC, a protein called TRBP, upon small pieces of RNA.

Source: Emory University